1010/16104-US1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: HOWARD WEINER

Serial No.: 07/460,852 Group Art Unit: 1815

Filed : February 21, 1990 Examiner: A. Mohamed

For : TREATMENT OF AUTOIMMUNE DISEASES BY ORAL ADMINISTRATION OF AUTOANTIGENS

May 18, 1993

I HEREBY CERTIFY THAT THIS PAPER OR, IF THIS PAPER IS A TRANSMITTAL LETTER, EVERY OTHER PAPER OR FEE REFERRED TO THEREIN IS BEING DEPOSITED WITH THE U.S. POSTAL SERVICE AS FIRST CLASS MAIL IN AN ENVELOPE ADDRESSED TO: COMMISSIONER OF PATENTS & TRADEMARKS, WASHINGTON, DC 20231.
ON MAY 18, 1993 (DATE OF DEPOSIT)
5-18-93 Henriette Mauro
DATE NAME

Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

LETTER

Sir:

Enclosed is the executed Declaration of Howard L. Weiner and its respective exhibits. Attached Exhibit A is an updated version of Dr. Weiner's Curriculum Vitae so it is slightly different than the one submitted with the unsigned declaration on 5/10/93. In addition, attached Exhibit B is the final version of the same article that accompanied the unsigned declaration.

Respectfully submitted,

Adda C. Gogoris
Reg. No. 29,714
Attorney for Applicant(s)

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New York, New York 10022
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Encls.: Declaration of Dr. Weiner and respective Exhibits

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#22
5/10/93

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: HOWARD WEINER

Serial No.: 07/460,852 Group Art Unit: 1815

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For : TREATMENT OF AUTOIMMUNE DISEASES BY ORAL ADMINISTRATION OF AUTOANTIGENS

I HEREBY CERTIFY THAT THIS PAPER OR THIS PAPER IS A TRANSMITTAL [illegible] OTHER PAPER OR FEE REFERRED TO HEREIN BEING DEPOSITED WITH THE [illegible] AS FIRST CLASS MAIL IN AN ENVELOPE ADDRESSED TO COMMISSIONER OF PATENTS & TRADEMARKS, WASHINGTON, DC 20231.
ON May 10, 1993 (DATE OF DEPOSIT)
5/10/93 C. Kaiazzi
DATE NAME

Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

DECLARATION OF HOWARD L. WEINER

I, HOWARD L. WEINER, do hereby declare and state as follows:

A. Introduction

1. I hold a M.D. degree, conferred by the University of Colorado in 1969.

2. I am employed as the Robert L. Kroc Associate Professor of Neurologic Diseases, Harvard Medical School, and I have held this position since 1985. I am also appointed as Physician, Medicine (Neurology), Brigham & Women's Hospital, Boston, MA, and I have had this appointment since 1987. Since 1985, I have been Co-Director of the Center for Neurologic Diseases at the same hospital.

3. I have extensive experience in the immunology of autoimmune diseases including in particular the oral enteral or by-inhalation use of antigens in the treatment of such diseases. A copy of my Curriculum Vitae is attached as Exhibit A.

4. I am a co-inventor of the subject matter described and claimed in this application, and I have reviewed the application, the Office Actions issued thereon, and the references cited in these Actions. I submit this declaration in rebuttal of the rejection of the application under 35 U.S.C. §§ 101, 112 and 103.

5. I am also a co-author of the a research article, to be published shortly in *Science*: Weiner et al., Double-Blind Pilot Trial of Oral Tolerization with Myelin Antigens in Multiple Sclerosis, *Science*, in press. A true copy of the preprint of this article accepted by *Science* is attached as Exhibit B.

B. Treatment of Multiple Sclerosis and Human Trial Results

6. The article reports the results of a double-blind study where bovine MBP is administered orally to human patients suffering from multiple sclerosis. As stated on page 3 of the preprint, footnote 15, a test group of patients were given a once daily oral dose of 300 mg of purified bovine MBP, while the control group received a placebo. Both groups were randomized for age, disease duration, extended disability status scale (EDSS), and number of exacerbations in the last two years.

7. The results of this trial show that the oral tolerization treatment had a positive effect on the test group. The number of myelin treated patients who had no major attacks during treatment was statistically significant, when compared to the placebo group. A subset of the test group, namely the males, had no major attacks during treatment, and had improved EDSS

scores, as well as improved physician impression and a reduced reliance on treatment with steroids. A second subset of the test group, those not expressing the HLA-DR2 phenotype (HLA-DR2$^-$), also showed significant improvement. None of the HLA-DR2$^-$ myelin treated patients had a major attack. This group also showed improved EDSS scores and improved physician impression. See, Exhibit B, page 1, col. 2-3, and page 2, tables 2 and 3.

C. Human Trials with Rheumatoid Arthritis Other Autoimmune Diseases

8. Moreover, a study supervised and controlled by one of my close collaborators, Dr. David Trentham, at the Beth Israel Hospital, involved the oral administration of collagen to 10 rheumatoid arthritis patients as detailed in Tables 1-10 of our co-pending patent application, Serial No. 07/951,565 (attached in Exhibit C, which is, in fact, an excerpt of this co-pending application (pp. 17-32). In this open-dosing study, 6 out of 10 patients received considerable benefit from oral collagen therapy as measured by reduction or elimination of most clinical symptoms and discontinuation or decrease of other drugs for several months post-treatment. Three of the 10 patients continue to function at the improved condition without further treatment. Two other patients experienced a relapse but after a single-month resumption of collagen therapy they resumed the improved state. A sixth patient seemed to be improving as well as the first three but follow-up was lost. A seventh patient experienced only a mild improvement and two other patients experienced no improvement but

were still able to discontinue cytotoxic drugs. The tenth patient withdrew from the study because of her poor initial condition, absence of improvement and remote location from the study center. Based on these positive results, a double-blind study has been undertaken.

9. Preliminary human clinical evidence was obtained, on information and belief, by another of my close collaborators, Dr. Nussenblatt of the National Eye Institute, Bethesda, MD. Dr. Nussenblatt administered S-antigen orally to two uveoretinitis patients and observed in one case considerable improvement in visual acuity. In this patient, steroids were discontinued after S-antigen therapy and has not resumed in several months. All previous attempts to discontinue steroids in this patient had been unsuccessful. In the other patient, Dr. Nussenblatt was also able to decrease steroids and other immunosuppressive medication after treatment with oral S-antigen.

D. <u>Diabetes</u>

10. In addition, a large clinical study involving the oral administration of insulin as an oral tolerizer to children at risk for Type 1 diabetes is being planned by Drs. George Eisenbarth and Richard Jackson, two of my close collaborators, at the Barbara Davis Diabetes Center in Denver, Colorado, and the Joslin Diabetes Center in Boston, respectively. Institutional Review Board approval has been received for this study which was designed and proposed based solely on rodent data (the NOD model for Type 1 diabetes). The sole reason this study has not already commenced is

that the U.S. Food and Drug Administration has not yet designated an approved supplier for the insulin to be used in this study.

11. Additional investigators also are interested in conducting similar studies. Dr. Noel Maclaren from Gainesville, Florida requested our collaboration: Dr. Maclaren is planning a large multi-center clinical trial for the prevention of insulin-dependent diabetes by oral administration of insulin. I submit that, on information and belief, neither my collaborators in diabetes as physicians and scientists nor the Review Boards of the institutions involved would undertake or sponsor such studies unless they believed they would be successful in humans.

12. In my opinion, these facts and data constitute adequate evidence to establish a utility of oral tolerization in the treatment of autoimmune disease in general, and, as evidenced by points 6-8, *supra*, specifically in multiple sclerosis and rheumatoid arthritis.

E. **The Prior Art Applied Against the Claims**

13. The prior art applied by the Examiner against the claims suffers from deficiencies such as the following:

Campbell is limited to intravenous administration of MBP and does not show a substantial benefit in humans. Campbell was published in 1973, yet no follow up of his work appeared in print as far as I am aware. Campbell proposed no mechanism for the treatment.

Whitacre (and her subsequent publications cited in the accompanying amendment) administered TSI, an anti-trypsin agent

to protect MBP from degradation. As a result, Whitacre did not induce tolerance through active suppression but appeared to be inducing tolerance through anergy ("antigen-specific unresponsiveness"). Because of this, a person of ordinary skill in the art could not extrapolate effectiveness of her results to humans. By contrast, my co-inventors and I were able to extrapolate our results to humans because we showed that we induced active suppression (by allowing our MBP to be degraded in the gut). As a result, we were able to see that events common to the human and rodent systems were in operation during the treatment we proposed, in that the method we invented would work in the same way as the development of tolerance to food antigens through food intake. Anergy on the other hand is a mechanism of immune suppression that has only begun to be elucidated now.

In addition to not postulating a mechanism that would enable her (and persons of ordinary skill) to extrapolate to humans, Whitacre worked only with an induced condition (EAE) induced by the same antigen as that employed to prevent it and did not show that her regime would have a benefit after disease induction.

The same deficiencies and limitations apply to Nagler-Anderson.

12. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements and the like so made are punishable by fine or imprison-

ment, or both, under Section 1001 of Title 18 of the United States Code and that such wilful false statements may jeopardize the validity of the present application or any patent issuing thereon.

Date

Howard L. Weiner

M:\1010\16104\AKW0670

CURRICULUM VITAE

Name:	Howard L. Weiner, M.D.
Address:	114 Somerset Road, Brookline, MA 02146
Date of Birth:	December 25, 1944
Place of Birth:	Denver, Colorado

Education:

1965	Dartmouth College, Hanover, New Hampshire
1969	University of Colorado School of Medicine

Postdoctoral Training:

1969-1970	Rotating Intern, Tel Hashomer Hospital, Israel
1970-1971	Medical Resident, Beth Israel Hospital, Boston
1970-1971	Clinical Fellow, Harvard Medical School
1971-1974	Resident in Neurology, Longwood Area Neurology Program
1971-1974	Clinical Fellow in Neurology, Harvard Medical School

Research Fellowships:

1972-1974	Research Fellow, Massachusetts General Hospital (Dr. Barry Arnason's laboratory)
1974-1976	Research Fellow, Immunology, University of Colorado Medical Center, Denver, Colorado (Dr. Henry Claman's laboratory)
1974-1976	Special Research Fellow of Colorado Multiple Sclerosis Society

Licensure and Board Certification:

1970	Massachusetts
1974	Colorado
1978	American Board of Psychiatry and Neurology

Academic Appointments:

1976-1977	Instructor in Neurology, Harvard Medical School
1977-1980	Assistant Professor of Neurology, Harvard Medical School
1980-1985	Associate Professor of Neurology, Harvard Medical School
1985-	Robert L. Kroc Associate Professor of Neurologic Diseases, Harvard Medical School

Academic Affiliations:

1984-	Affiliate Member of the Program in Neuroscience, Harvard Medical School

Hospital Appointments:

1977-1987	Associate in Medicine (Neurology), Brigham and Women's Hospital
1977-1985	Research Associate in Neuroscience, The Children's Hospital
1987-1991	Physician, Medicine (Neurology), Brigham and Women's Hospital
1992-	Senior Physician, Medicine (Neurology), Brigham and Women's Hospital

Awards and Honors:

1969	University of Colorado School of Medicine Phi Delta Epsilon Award for Academic Excellence and Merck Award in Medicine
1974-1976	Research Fellowship, Colorado Multiple Sclerosis Society
1976-1977	NIH Special Research Fellowship
1977-1982	NIH Teacher Investigator Award, National Institute of Neurological and Communicative Disorders and Stroke (NINCDS)
1985	Recipient of Robert L. Kroc Chair in Neurology for Multiple Sclerosis Research, Awarded by Kroc Foundation, Santa Inez, California.
1988-1995	NIH Jacob Javits Neuroscience Investigator Award (Seven year Merit Award, NINCDS)

Major Committee Assignments:

1976-	Scientific Advisory Board, Massachusetts Multiple Sclerosis Society
1980-1983	Ad Hoc Member, Clinical Research Center Review Study Section, NIH
1982-1987	National Multiple Sclerosis Society Scientific Advisory Board, Committee on Research on the Etiology, Diagnosis, Natural History, Prevention and Therapy of Multiple Sclerosis
1982-1989	National Multiple Sclerosis Society Committee on Working Trials of New Drugs in MS
1983-1985	New Pathways Project, Harvard Medical School, Resource Representative for the Department of Neurology
1984	Ad Hoc Member, Virology Study Section, NIH

Editorial Boards:

1984-	Editorial Board, Journal of Neuroimmunology
1984-1988	Editorial Board, Journal of Molecular and Cellular Immunology
1989-	Editorial Board, Journal of Autoimmunity

Professional Societies:

1976	American Academy of Neurology
1976	American Society for Microbiology
1976	American Association for the Advancement of Science
1977	American Association of Immunologists
1981	American Neurologic Association

Major Research Interests:

1. Immunology and immunotherapy of multiple sclerosis

2. Mechanisms of autoimmunity
3. Neuroimmunology
4. Oral tolerance

Teaching Experience:

1977-1989	Annual Intensive Clinical Neurology Course, New York City
1977-1987	Neuropathology 711, Department of Neuroscience, Harvard Medical School
1977-	Introduction to Clinical Medicine, Brigham and Women's Hospital
1977-	Harvard Continuing Education Courses: Neurology, Immunology, Pediatric Neurology, Scientific Foundations of Internal Medicine
1978-1987	Pathophysiology of the Nervous System - HST 131J
1981-1983	Lecturer, Neuroimmunology Course, Annual Meeting of the American Academy of Neurology
1984-1987	Chairman, Neuroimmunology Course, Annual Meeting of the American Academy of Neurology
1984-	Neurobiology of Disease, Department of Neurobiology, Harvard Medical School
1988	Chairman, FASEB Autoimmunity Conference, Saxton's River, VT
1989	Co-Chairman, International Conference on Therapy and Diagnosis of Multiple Sclerosis (National MS Society, Jekyll Island)

Principle Clinical and Hospital Service Responsibilities:

1976-	Attending physician, Brigham and Women's Hospital Neurology Service
1976-	Consulting physician, Beth Israel Hospital and Children's Hospital Neurology Services
1980-	Director, Multiple Sclerosis inpatient and outpatient clinical services, Brigham and Women's Hospital
1985-	Co-Director, Center for Neurologic Diseases, Brigham and Women's Hospital

A. Original Communications

1. Weiner, H.L. and Robinson, W.A.: Leukopoietic activity in human urine following operative procedures. Proc. Soc. Exp. Biol. Med. 136: 29- 33, 1971.

2. Weiner, H.L., Moorhead, J.W. and Claman, H.N.: Anti-immunoglobulin stimulation of murine lymphocytes. I. Age dependency of the proliferative response. J. Immunol. 116: 1565-1661, 1976.

3. Weiner, H.L., Moorhead, J.W., Yamaga, K. and Kubo, R.: Anti- immunoglobulin stimulation of murine lymphocytes. II. Identification of cell surface target molecules and requirements for cross linkage. J. Immunol. 117: 1527-1533, 1976.

4. Caplan, L.R., Weiner, H.L., Weintraub, R.M. and Austen, W.G.: "Migrainous" neurological dysfunction in two patients with prosthetic cardiac valves. Headache 16: 218-221, 1976.

5. Weiner, H.L., Scribner, D.J. and Moorhead, J.W.: Anti-immunoglobulin stimulation of murine lymphocytes. III. Enhancement of the development of responsive B cells by thymic deprivation. Cell Immunol. 31: 77-84, 1977.

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10. Weiner, H.L., Schocket, A.L. and Lehrich, J.R.: Lymphocytotoxic antibodies in subacute sclerosing panencephalitis and amyotrophic lateral sclerosis. Lancet 1: 1013-1014, 1977.

11. Opelz, G., Terasaki, P., Myers, L., Ellison, G., Ebers, G., Zabriskie, J., Weiner, H., Kempe, H., and Sibley, W.: The association of HLA antigens A3, B7 and DW2 with 330 multiple sclerosis patients in the United States. Tissue Antigens 9: 54-58, 1977.

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14. Weiner, H.L., Scribner, D.J., Schocket, A.I. and Moorhead, J.W.: Increased proliferative response of human peripheral blood lymphocytes to anti-immunoglobulin antibodies in elderly people. Clin. Immunol. Immunopathol. 9: 356-363, 1978.

15. Ault, K.A. and Weiner, H.L.: Isolation and characterization of the class of human blood lymphocytes responsible for antibody-dependent cellular cytotoxicity. Clin. Immunol. Immunopathol. 11: 60-76, 1978.

16. Weiner, H.L., Cherry, J., and McIntosh, K.: Decreased lymphocyte transformation to vaccinia virus in multiple sclerosis. Neurology 28: 415-420, 1978.

17. Schocket, A.L. and Weiner, H.L.: Lymphocytotoxic antibodies in family members of patients with multiple sclerosis. Lancet 1: 571-573, 1978.

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55. Epstein, R.L., Finberg, R., Powers, M.L., and Weiner, H.L.: Interaction of reovirus with cell surface receptors. IV. The reovirus type 3 receptor is expressed predominantly on murine Lyt-2,3+ and human T8 cells. J. Immunol. 133: 1614-1617, 1984.

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61. Hafler, D.A., Buchsbaum, M., Johnson, D., and Weiner, H.L.: Phenotypic and functional analysis of T-cells cloned directly from the blood and cerebrospinal fluid of patients with multiple sclerosis. Ann. Neurol. 18:451-458, 1985.

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EXAMPLES

For the purposes of the two studies conducted and described below, the patient's arthritic state was measured utilizing several different criteria such as subjective pain, gross anatomical observations, timing of physical acts and subjective well-being as described by the patient. Gross anatomical observations included AM stiffness, grip strength and number of swollen joints and were made during monthly examinations by a physician of the arthritic joints before and during type I collagen treatment as compared with the same joints prior to treatment.

Monthly data measuring subjective pain involved applying gently pressure to each arthritic joint in turn by a physician and being told by the patient whether pain was experienced.

Morning stiffness data were based on the patient's experience and reports on how long it took for their arthritic joints to become physically limber. Additionally, grip strength for each hand was measured each month with a standard mercury sphygmomanometer with the cuff inflated to 20 mm Hg. Finally, the patients were timed to measure how many seconds were needed to complete a 50 foot walk.

Global assessment (P = poor; F = fair; G = good; VG = very good; and VP = very poor) was subjectively made by the attending physician. Progress was similarly subjectively assessed (B = better; W = worse; MB = medium better; MW = medium worse, S = same).

NSAID stands for "nonsteroidal antiinflammatory drugs"; RF stands for "rheumatoid factor"; ESR stands for "erythrocyte sedimentation rate"; HCT stands for "hematocrit"; bid stands for "twice a day"; qid and qd stand for "per day"; IA stands for "intra-joint".

Daily dosage of whole type II chick collagen protein consumed was 0.1 milligrams for the first month and 0.5 milligrams for each subsequent month of treatment.

EXAMPLE 1:

Water-soluble purified whole chick Type II collagen protein was obtained from commercial sources; (Genzyme, Boston, MA) or was purified according to the procedure of Trentham, D. et al., J. Exp. Med. 146:857, 1977. Patients, LS, MF, NS and CO, suffering from arthritis were given a solution of whole type II collagen protein in 0.01M acetic acid 0.1 or 0.5 mg/ml collagen. The patients were instructed to consume daily on an empty stomach a predetermined volume corresponding to 0.1 milligrams for the first month of treatment and 0.5 mg to all subsequent months of treatment. Most of the patients added the predetermined amount of type II collagen protein to orange juice to maintain solubility and shortly consumed the mixture.

Collagen treatment was discontinued after three months if the patient reported (and if the physician agreed) a substantial improvement. However, type II collagen treatment was subsequently resumed when a patient reported a relapse into the arthritic state. Monthly data gathered for each of the above

patients are summarized in Tables 1 - 4.

Table 1 is a summary of data gathered measuring the arthritic disease state of patient 1, LS a 30-year old female. Prior drug treatment of auranofin was discontinued during the present study. Surprising recovery from arthritis during the second month of collagen treatment prompted discontinuation of further therapy. Feldene (piroxicam) was administered during months 8 and 9 after collagen therapy initiation.

Substantial improvement was observed after the first month of treatment with whole type II collagen protein. Complete recovery was observed on the second month of treatment, but some weakness was still observed in the grip strength test. This muscular weakness may have been caused by the prolonged disuse and atrophy of the muscles from the arthritic pain of the joints. On the third month of treatment, there was residual arthritis observed in one joint of the right hand which remained swollen, tender to slight pressure, the source of morning stiffness, and the reason for a weakened right hand grip. However, the joints in the left hand remain free of arthritis and the 50 foot walk was normal.

Treatment was discontinued for three and a half months, but reinstated on the seventh month when the patient LS experienced a mild arthritic relapse involving six joints in both hands. Ambulatory motion was not affected by this relapse. The patient was able to complete the 50 foot walk in normal time.

Treatment was reinstated at the normal daily dose of

0.5 milligrams. Again, remarkable recovery from the arthritic disease state was observed within a month with only residual arthritis present in one right hand joint. Grip strength doubled from that observed during the relapse.

Treatment was continued for one more month where patient LS exhibited the highest grip strength for both hands observed during the study, in spite of the remaining one arthritic joint in the left hand. After three month of collagen treatment to address the relapse, further treatment was again discontinued. To date, four months have passed without patient LS succumbing to or manifesting any clinical evidence of arthritis, other than the limited manifestation on a single right hand joint. Grip strength for both hands has decreased slightly.

Table 2 is a summary of the progress of a female patient, MF (23) participating in the same study as patient LS. Prior drug treatment with methotrexate was discontinued. Patient MF was observed to experience a surprising freedom from symptoms after the first month of treatment with a daily dosage of 0.1 milligrams of whole type II collagen protein for one month followed by 0.5 mg for two months. Complete recovery was observed after the second month of treatment. No recurrence of arthritis was observed during the subsequent eleven months.

Table 3 summarizes the data for a third patient in the study, female NS (50). Methotrexate treatment was discontinued during this study. Remarkable diminution of symptoms was observed during the first month of treatment with collagen

protein. The number of swollen joints was reduced from five to one, while all tender joints exhibited complete recovery. Morning stiffness was reduced from 120 minutes to 15 minutes, but only left hand grip strength showed a slight improvement. Residual swelling was observed on a single joint in the right hand, but complete recovery was observed in all other previously affected joints. Complete recovery was achieved during the third month of collagen treatment and further treatment was discontinued in spite of occasional arthritic flare-ups.

Table 4 encapsulates the data from patient CO (a female, 42) the last participant of this study. A more gradual recovery from arthritis was observed compared to other patients. Half of the affected joints recuperated from arthritic swelling and tenderness after the first month of collagen treatment, but morning stiffness, grip strength for both hands and length of time to complete the 50 foot walk remained substantially the same as the disease state. Remarkable recovery was recorded during the second month of treatment and almost complete recovery was observed during the third month, barring a single tender joint and some slight ambulatory weakness in the 50 foot walk test. Treatment was discontinued for the next two months, but was reinstated when patient CO experienced a partial relapse during the fifth month. After three more months of further treatment, patient CO has also completely recovered from arthritis, to date.

PATIENT 1 (LS)*

	Month										
	0	1	2	3	4	5	6	7	8	9	12
date	2/6/91	2/27/91	3/20/91	4/26/91			8/2/91	9/5/91	10/21/91	12/06/91	2/19/92
Dose (mg)		0.1	0.5	0.5	0	0	0.5	0.5	0.5	0	0
No. swollen joints	7	2	0	1	1	1	6	1	1	1(_-R wrist)	1(_-R wrist)
No. tender joints	9	2	0	1	1	1	6	1	0	0	0
AM stiffness (min)	60	60	0	15	0	40-60	60	0	0	0	0
Grip strength (mm)											
R	60	55	88	72	120	86	70	75	140	102	130
L	45	43	85	110	95	128	85	145	148	102	122
50' walk (sec)	16	16	9	9	9	9	9	9	9	9	9
Pt. global assessment	P	F	VG	G	VG	VG	F	G	VG	VG	VG
Progress	Same	MB	Same	Same				B	B	B	Same
NSAID			+	+	-	-	-	+ (Feldene)	+ (Feldene)	+ (1 mo) Tr. swelling R wrist; 4 mi/AM walks	- working full time
Other											
RF (date)	2/13/91 neg	3/6/91 neg	3/28/91 equiv.		5/8/91 neg				+ 1:320		

* Drug discontinued - Auranofin
Course I (initial) 2/6/91, final 5/5/91
Course II (initial) 8/2/91, final 11/2/91

PATIENT 2 (MF)*

	Month									
	0	1	2	3	4	5	6	7	8	12
date	2/21/91	3/27/91	4/18/91?	5/29/91	6/26/91				10/23/91	02/20/92
Dose (mg)		0.1	0.5	0.5	0	0	0	0	0	0
No. swollen joints	3	1	0	0	0				0	0
No. tender joints	3	0	0	0	0				0	0
AM stiffness (min)	60	30	0	0	0				0	0
Grip strength (mm)										
R	240	244	245	280	280				280	280
L	180	238	242	275	280				280	280
50' walk (sec)	14	11	9	9	9				9	9
Pt. global assessment	P	G	G	VG	VG				VG	VG
Progress		B	B	B	B				Same	Same
NSAID	+	+	+	-	-				-	-
Other										
RF (date)	2/8/91 neg	3/27/91 neg		5/29/91 neg					10/29/91 neg	

* Drug discontinued - MTX
Course I (initial) 2/22/91, final 5/26/91

PATIENT 3 (NS)*

	Month							
	0	1	2	3	4	5	6	#10
date	4/4/91	5/2/91	6/6/91	7/1/91?		9/19/91	10/24/91	02/20/92
Dose (mg)		0.1	0.5	0.5	0	0	0	0
No. swollen joints	5	1	1	0	0	1	1	1
No. tender joints	5	0	0	0	2	1	0	0
AM stiffness (min)	120	15	0	0	0	0	15	15
Grip strength (mm)								
R	90	90	135	138	138	128	130	136
L	76	82	135	138	138	192	190	186
50' walk (sec)	17	13	12	12	12	12	12	13
Pt. global assessment	P	F	VG	VG	F	VG	VG	VG
Progress		B	B	B		B	Same	Same
NSAID	+	+	↓	+	+		+	+
Other					(Motrin)	(Motrin x3)	(Motrin 2x3) Right knee Tr. swollen	Same as month 6
RF (date)	3/27/91 neg					neg		

* Drug discontinued - MTX
Course I (initial) 4/4/91, final 7/5/91

PATIENT 4 (CO)*

	Month									
	0	1	2	3	4	5	6	7	8	9
date	5/3/91	6/3/91	7/3/91	8/30/91		10/4/91	10/25/91	11/22/91	12/20/91	2/03/92
Dose (mg)		0.1	0.5	0.5	0	0	0.5	0.5	0.5	0
No. swollen joints	8	4	2	0	1	4	10	2	0	0
No. tender joints	9	5	2	1	0	6	12	2	0	0
AM stiffness (min)	120	120	15	<15	0	120	120	30	<15	0
Grip strength(mm)										
R	58	45	82	92	70	54	52	45	50	45
L	48	42	68	78	60	50	52	45	52	55
50' walk (sec)	9	9	9	9	10	13	16	13	12	12
Pt. global assess-ment	P	P	F	G	VG	F	VP	MB	MB	MB
Progress		Same	B	MB	MB	W	W	VG	VG	VG
NSAID	+	+	+ (Voltaren)	+ (Voltaren)	+ (Voltaren)	+ (Voltaren 75-bid; Advil)	+ (Voltaren)	V-bid	V-bid	V-bid
Other									energy good	
RF (dose)	4/24/91 1:320				10/9/91 1:5120	10/29/91 1:1280				

* Drug discontinued - MTX
Course I (initial) 5/3/91, final 8/3/91
Course II (initial) 10/25/91, final 1/25/91

EXAMPLE 2

The same preparation dosage and protocol were used as in Example 1. Patients ML, MT, RB, LM, DH and SH suffering from rheumatoid arthritis were given chick type II collagen as in Example 1 and were monitored as in Example 1. All of these patients were also treated in a single-blind manner; their condition was worse than that of the Example 1 patients and their average age was about 9 years higher. One female patient (DH) withdrew because of no progress and inconvenience of travel.

Tables 5 - 10 summarize the data collected for 6 additional individual patients (5 females, 1 male) involved in a second on-going study on the effectiveness of oral administration of whole type I collagen protein to suppress or cure arthritis. Only patient RB (Table 7) experienced complete recovery. A second patient has withdrawn from the present study. The other patients have not experienced as remarkable a recovery as those patients involved in the first study, figures 1 - 4. There has been great improvement from arthritis, but the rate of recovery is more gradual. More time is needed to effectively evaluate the effects of the second study, but all of the patients of the second study had much more severe disease than the patients in the first study. Moreover, the second group of patients were generally older than the first (ages were 23, 36, 52, 55, 55 and 65). Nevertheless, patients 5 and 7 benefitted considerably and even patients 8 and 10 were

able to discontinue use of cytotoxic drugs.

PATIENT 5 (ML)*

	Month									
	0	1	2	3	4	5	6	7	8	9
date	8/9/91	9/5/91	10/3/91	10/31/91						
Dose (mg)		0.1	0.5	0.5						
No. swollen joints	12	6	5	4						
No. tender joints	16	6	5	2						
AM stiffness (min)	All day	120	120	30						
Grip strength (mm)										
R	22	44	70	75						
L	26	38	45	13						
50' walk (sec)	19	15	15	15						
Pt. global assessment	VP	P	VG	G						
Progress		Same	B	B						
NSAID	+ (Clinoril & Pred)	+	+	decrease Pred-2.5 mg 0-Naprosyn						
Other		0.9cm module								
RF (date)	8/5/91 1:5120	10/3/91	10/31/91 1:5120	1:5120						

* Drug discontinued - MTX
Course I (initial) 8/5/91, final 11/2/91

PATIENT 6 (MT)*

	Month									
	0	1	2	3	4	5	6	7	8	9
date	8/21/91	9/19/91	10/17/91	11/13/91						
Dose (mg)		0.1	0.5	0.5	0					
No. swollen joints	12	12	8	7						
No. tender joints	14	14	10	10						
AM stiffness (min)	All day	All day	till 2 pm	All day						
Grip strength (mm)										
R	18	28	30	8						
L	30	38	35	18						
50' walk (sec)	18	18	18	23						
Pt. global assessment	P	P	P	VP						
Progress	Same	Same	W							
NSAID	Naprosyn (750)	+	+Pred	increase Pred-5mg: Naprosyn-375bid						
Other	ESR-22 Hct-36									
RF (date)	8/21/91 1:640			11/13/91 +						

* Drug discontinued - MTX-2 wks
Pred-2.5 mg during 0.1-early 0.5, resumed
Course I (initial) 8/21/91, final 11/21/91

PATIENT 7 (RB)*

	Month									
	0	1	2	3	4	5	6	7	8	9
date	8/21/91	9/20/91	10/18/91	12/05/91	01/15/92					
Dose (mg)		0.1	0.5	0.5	0					
No. swollen joints	14	8	4	1	0					
No. tender joints	16	4	6	0	0					
AM stiffness (min)	120	90	90	0	60					
Grip strength (mm)										
R	68	92	92	105	95					
L	40	70	70	85	85					
50' walk (sec)	16	11	11	11	11					
Pt. global assessment	VP	MB	G	VG	VG					
Progress		MB	Same	B	Same					
NSAID	Naprosyn (1500)	+ (1000)	+ (1000) (Tyl-3am, 2pm) Pred	+ Tyl-2bid Pred-2mgqd	+ Pred-2mgqd Nap-55bid					
Other 5mm nodule R-olecranon Pred-3mg/da			3mm module	Unchg'd	Same					
RF (date)	8/21/91 1:5120	9/24/91 1:160	10/22/91 1:10240							

* Drug discontinued - Imuran
Course I (initial) 8/21/91, final 11/21/91

PATIENT 8 (LM)*

	Month									
	0	1	2	3	4	5	6	7	8	9
date	10/3/91	11/1/91	12/5/91	1/9/92						
Dose (mg)		0.1	0.5	0.5	0					
No. swollen joints	10	10	8	9						
No. tender joints	14	14	10	10						
AM stiffness (min)	180	120	150	120						
Grip strength (mm)										
R	30	52	38	35						
L	28	42	28	32						
50' walk (sec)	22	23	22	20						
Pt. global assessment	P	P	P	P						
Progress		Same	Same	Same						
NSAID	Naprosyn bid Darvocet	Nap-250bid Darvocet	Nap Darvocet							
Other	IA steroids/ both knees 2 wks ago									
RF (date)	10/8/91 1:160									

* Drug discontinued - MTX
Course I (initial) 10/3/91, final 1/3/92

PATIENT 9 (DH)*

	Month									
	0	1	2	3	4	5	6	7	8	9
date	10/23/91	11/22/91								
Dose (mg)		0.1	0.5	0.5						
No. swollen joints	12	12		Withdrew from trial 1/3/92						
No. tender joints	14	13								
AM stiffness (min)	240	360								
Grip strength (mm)										
R	50	5								
L	35	10								
50' walk (sec)	23	in wheel chair								
Pt. global assessment	P	VP								
Progress		MW								
NSAID	Disalc-750qid Pred-4mg	Pred increase 10mg/qid								
Other										
RF (date)	neg.									

* Drug discontinued - Mtx,-17.5 mg-off 8 da;had PM fatigue
Course I (initial) 10/24/91, final 1/24/92

PATIENT 10 (SH)*

	Month									
	0	1	2	3	4	5	6	7	8	9
date	10/26/91	11/22/91	12/19/92	2/6/92						
Dose (mg)		0.1	0.5	0.5						
No. swollen joints	14	11	11	11						
No. tender joints	16	11	13	13						
AM stiffness (min)	480	360	360	360						
Grip strength (mm)										
R	28	25	12	22						
L	30	35	28	26						
50' walk (sec)	23 (with cane)	23	22	22						
Pt. global assessment	VP	P	P	P						
Progress		Same	Same	Same						
NSAID										
Other	Pred-10mgqd 6x500-Disalcid			Pred decrease 5mg						
RF (date)	1:320									

* Drug discontinued - 6-MP
Course I (initial) 10/26/91, final 1/26/91

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